

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

FOREST LABORATORIES, INC.,  
FOREST LABORATORIES HOLDINGS,  
LTD., MERZ PHARMA GMBH & CO.  
KGAA, and MERZ PHARMACEUTICALS  
GMBH,

Plaintiffs,

V.

APOTEX INC. and APOTEX CORP.,  
Defendants.

C.A. No. \_\_\_\_\_

## COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively “Plaintiffs”) for their Complaint against Defendants Apotex Inc. and Apotex Corp. (collectively “Defendants”) hereby allege as follows:

**PARTIES**

1. Plaintiff Forest Laboratories, Inc. (“Forest Labs”) is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as “Forest”).

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as “Merz”).

5. Upon information and belief, Defendant Apotex Corp. (“Apotex USA”) is a Delaware corporation, and the wholly-owned subsidiary and agent of Defendant Apotex Inc., having a principal place of business at 2400 N. Commerce Parkway, Weston, Florida, 33326.

6. Upon information and belief, Defendant Apotex Inc. (“Apotex”) is a Canadian corporation having a principal place of business at 150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9. Upon information and belief, Defendant Apotex, itself and through its wholly-owned subsidiary and agent Defendant Apotex USA, manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

#### **NATURE OF THE ACTION**

7. This is a civil action for infringement of United States Patent No. 5,061,703 (“the ‘703 patent”) (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100 *et seq.*

#### **JURISDICTION AND VENUE**

8. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or

participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including Plaintiff Forest Labs, a Delaware corporation. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

10. This Court has personal jurisdiction over Defendant Apotex USA by virtue of the fact that, *inter alia*, Apotex USA is a Delaware corporation.

11. This Court has personal jurisdiction over Defendant Apotex by virtue of, *inter alia*: (1) its presence in Delaware through its subsidiary and agent Apotex USA; and (2) its systematic and continuous contacts with Delaware, including through its subsidiary and agent Apotex USA.

12. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

#### THE PATENT-IN-SUIT

13. On October 29, 1991, the ‘703 patent, titled “Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia,” was duly and legally issued by the United States Patent and Trademark Office (“PTO”). Merz has been, and continues to be, the sole assignee of the ‘703 patent since its issuance.

14. Forest is the exclusive licensee of the ‘703 patent in the United States. Forest holds New Drug Application (“NDA”) No. 21-487 for Namenda® brand memantine hydrochloride tablets. The ‘703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (“Orange Book”) for Namenda®.

15. Forest is the exclusive distributor of Namenda® in the United States.

16. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

**ACTS GIVING RISE TO THIS ACTION**

**Infringement Of The '703 Patent By  
Defendants Apotex And Apotex USA**

17. Upon information and belief, Defendant Apotex, through its subsidiary and agent Apotex USA, submitted ANDA No. 90-244 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Apotex Generic Products"). ANDA No. 90-244 specifically seeks FDA approval to market the Apotex Generic Products prior to the expiration of the '703 patent.

18. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Apotex alleged in ANDA No. 90-244 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Apotex Generic Products. Plaintiffs received written notification of ANDA No. 90-244 and its § 505(j)(2)(A)(vii)(IV) allegation on or about April 23, 2008.

19. Apotex's submission of ANDA No. 90-244 to the FDA, through its subsidiary and agent Apotex USA, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Apotex commercially manufactures, uses, offers to sell, sells, or imports any of the Apotex Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

20. Apotex USA is jointly and severally liable for any infringement of the '703 patent. Upon information and belief, Apotex USA participated in, contributed to, aided, abetted and/or induced Apotex's submission of ANDA No. 90-244 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

21. Apotex USA's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 90-244 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Apotex USA commercially manufactures, uses, offers to sell, sells, or imports any of the Apotex Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

22. Apotex and Apotex USA were aware of the '703 patent prior to filing ANDA No. 90-244.

23. Apotex's and Apotex USA's actions render this an exceptional case under 35 U.S.C. § 285.

24. Plaintiffs will be irreparably harmed by Apotex's and Apotex USA's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

#### **PRAYER FOR RELIEF**

**WHEREFORE**, Plaintiffs pray for judgment as follows:

- A. That Apotex and Apotex USA have infringed the '703 patent;
- B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Apotex's and Apotex USA's ANDA No. 90-244 identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Apotex and Apotex USA, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

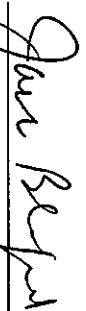
E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

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# EXHIBIT A

**United States Patent** [19][11] Patent Number: **5,061,703**

Bormann et al.

[45] Date of Patent: **Oct. 29, 1991**[54] **ADAMANTANE DERIVATIVES IN THE  
PREVENTION AND TREATMENT OF  
CEREBRAL ISCHEMIA**[75] Inventors: Joachim Bormann, Frankfurt;  
Markus R. Gold, Naunheim, Wolfgang  
Sebatton, Eschborn, all of Fed. Rep.  
of Germany[73] Assignee: Merz + Co. GmbH & Co., Frankfurt  
am Main, Fed. Rep. of Germany

[21] Appl. No.: 508,109

[22] Filed: Apr. 11, 1990

[30] Foreign Application Priority Data

Apr. 14, 1989 [EP] European Pat. Off. .... 89106657

[51] Int. Cl.<sup>5</sup> ..... A61K 31/13; A61K 31/41;  
A61K 31/35; A61K 31/445[52] U.S. Cl. .... 514/212; 514/325;  
514/359; 514/662

[58] Field of Search ..... 514/212, 325, 359, 662

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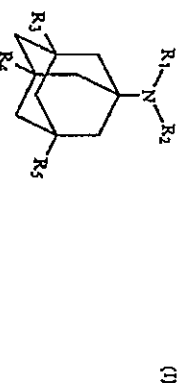
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*Primary Examiner*—Stanley J. Friedman  
*Attorney, Agent, or Firm*—Gordon W. Hueschen

## [57] ABSTRACT

A method for the prevention and treatment of cerebral  
ischemia using an adamantane derivative of the formula

wherein

R<sub>1</sub> and R<sub>2</sub> are identical or different, representing hydro-  
gen or a straight or branched alkyl group of 1 to 6 C  
atoms or, in conjunction with N, a heterocyclic  
group with 5 or 6 ring C atoms;

wherein

R<sub>3</sub> and R<sub>4</sub> are identical or different, being selected from  
hydrogen, a straight or branched alkyl group of 1 to  
6 C atoms, a cycloalkyl group with 5 or 6 C atoms,  
and phenyl;

wherein

R<sub>5</sub> is hydrogen or a straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl  
group,or a pharmaceutically-acceptable salt thereof, is dis-  
closed.**13 Claims, No Drawings**

Reaction scheme according to formula (I) are pre-  
the following reaction scheme:

### Reaction scheme



5  
Ad-Hal  
↓ alkylation (R<sub>3</sub>)  
alkylation (R<sub>4</sub>)  
alkylation (R<sub>5</sub>) R<sub>5</sub>

10 Ad-R<sub>3</sub> → → Ad-R<sub>3</sub> → → Ad-R<sub>3</sub>  
HCONH<sub>2</sub> R<sub>4</sub> HCONH<sub>2</sub> R<sub>4</sub> HCONH<sub>2</sub>

15 ↓ ↓ ↓  
H<sup>+</sup>/H<sub>2</sub>O H<sup>+</sup>/H<sub>2</sub>O H<sup>+</sup>/H<sub>2</sub>O

20 NH<sub>2</sub> NH<sub>2</sub> NH<sub>2</sub>  
Ad-R<sub>3</sub> Ad-R<sub>3</sub> R<sub>5</sub>-Ad-R<sub>3</sub>  
R<sub>4</sub> R<sub>4</sub> R<sub>4</sub>

Introduction of R<sub>1</sub>/R<sub>2</sub> alternatively

**25 Introduction of Ad = adamantyl group**

$$\begin{array}{c}
 \text{NH}_2 \\
 | \\
 \text{Ad} \rightarrow \text{R}_3
 \end{array}
 \xrightarrow{\text{H}^+/\text{H}_2\text{O}}
 \begin{array}{c}
 \text{NH}_2 \\
 | \\
 \text{Ad} \rightarrow \text{R}_3 \\
 | \\
 \text{R}_4
 \end{array}
 \xrightarrow{\text{H}^+/\text{H}_2\text{O}}
 \begin{array}{c}
 \text{NH}_2 \\
 | \\
 \text{R}_5 \rightarrow \text{Ad} \rightarrow \text{R}_3 \\
 | \\
 \text{R}_4
 \end{array}$$

Alkylation of the halogenated adamantanes can be achieved by known methods, for example, through Friedel-Crafts reaction (introduction of phenyl group), or by reaction with vinylidene chloride, subsequent reduction and suitable Wittig reaction of the aldehydes and subsequent hydration, or by introduction of ethylene and subsequent alkylation with appropriate cuprates, or by introduction of ethylene and reduction of the halogen alkyl adamantanes, or by acylation with  $\text{CO}_2$  and reduction of the carboxylic acid.

**CO<sub>2</sub> and reduction of the carboxylic acid.**

The compounds according to formula (I) known

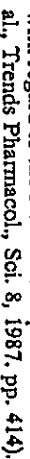
45 the dopamine/acetylcholine system.

In contrast to this type of disease, cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas (Rothmann & Olney, *Trends Neurosci* 10, 1989, pp. 239).

Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels (Kemp et al., *Trends Pharmacol., Sci.* 8, 1987, pp. 414).

Such intervention can, for example, be effected using

al., *Trends Pharmacol., Sci.* 8, 1987, pp. 414).



60 EP-A 0 264 183.

These heterocyclic, aromatic compounds are lipophilic and exhibit NMDA receptor channel-antagonistic and anticonvulsive properties. They are prepared by a relatively expensive method generating enantiomeric mixtures which may be split into the individual optical antipodes.

The present invention is aimed at preparing and employing compounds which can be chemically generated

by simple methods, exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of cerebral ischemia.

This objective can be achieved according to the invention by using the 1-amino adamantanes of formula (I).

It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia. Therefore, the adamantane derivatives of formula (I) are especially suited for the prevention and treatment of cerebral ischemia after apoplexy, open-heart surgery, cardiac standstill, subarachnoid hemorrhage, transient cerebro-ischemic attacks, perinatal asphyxia, anoxia, hypoglycemia, apnoea and Alzheimer's disease. The amount employed is a cerebral ischemia-alleviating or preventive amount.

Examples of compounds prepared and used according to the invention are:

1-amino adamantane  
1-amino-3-phenyl adamantane  
1-amino-methyl-adamantane  
1-amino-3,5-dimethyl adamantane (test compound no. 1)  
1-amino-3-ethyl adamantane (test compound no. 2)  
1-amino-3-propyl adamantane (test compound no. 3)  
1-amino-3-n-butyl adamantane  
1-amino-3,5-diethyl adamantane (test compound no. 4)  
1-amino-3,5-diisopropyl adamantane  
1-amino-3,5-di-n-butyl adamantane  
1-amino-3-methyl-5-ethyl adamantane  
1-N-methylamino-3,5-dimethyl adamantane (test compound no. 5)  
1-N-ethylamino-3,5-dimethyl adamantane (test compound no. 6)  
1-N-isopropyl-amino-3,5-dimethyl adamantane  
1-N,N-dimethyl-amino-3,5-dimethyl adamantane  
1-N-methyl-N-isopropyl-amino-3-methyl-5-ethyl adamantane  
1-amino-3-butyl-5-phenyl adamantane  
1-amino-3-pentyl adamantane  
1-amino-3,5-dipentyl adamantane  
1-amino-3-pentyl-5-hexyl adamantane  
1-amino-3-pentyl-5-cyclohexyl adamantane  
1-amino-3-pentyl-5-phenyl adamantane  
1-amino-3-hexyl adamantane  
1-amino-3,5-dihexyl adamantane  
1-amino-3-hexyl-5-cyclohexyl adamantane  
1-amino-3-hexyl-5-phenyl adamantane  
1-amino-3-cyclohexyl adamantane (test compound no. 7)  
1-amino-3,5-dicyclohexyl adamantane  
1-amino-3-cyclohexyl-5-phenyl adamantane  
1-amino-3,5-diphenyl adamantane  
1-amino-3,5,7-trimethyl adamantane  
1-amino-3,5,7-trimethyl-7-ethyl adamantane (test compound no. 8)  
1-amino-3,5-diethyl-7-methyl adamantane  
1-N-piperidino and 1-N-piperidine derivatives,  
1-amino-3-methyl-5-propyl adamantane  
1-amino-3-methyl-5-pentyl adamantane  
1-amino-3-methyl-5-hexyl adamantane  
1-amino-3-methyl-5-cyclohexyl adamantane  
1-amino-3-methyl-5-phenyl adamantane  
1-amino-3-ethyl-5-propyl adamantane  
1-amino-3-ethyl-5-butyl adamantane  
1-amino-3-ethyl-5-pentyl adamantane

1-amino-3-ethyl-5-hexyl adamantane  
1-amino-3-ethyl-5-cyclohexyl adamantane  
1-amino-3-ethyl-5-phenyl adamantane  
1-amino-3-propyl-5-butyl adamantane  
1-amino-3-propyl-5-pentyl adamantane  
1-amino-3-propyl-5-hexyl adamantane  
1-amino-3-propyl-5-cyclohexyl adamantane  
1-amino-3-propyl-5-phenyl adamantane  
1-amino-3-butyl-5-pentyl adamantane  
1-amino-3-butyl-5-hexyl adamantane  
1-amino-3-butyl-5-cyclohexyl adamantane  
1-amino-3-butyl-5-phenyl adamantane  
1-amino-3-butyl-5-ethyl adamantane  
1-amino-3-butyl-5-hydrogen such as, for example, their N-methyl, N,N-dimethyl, N-ethyl, N-propyl derivatives and their acid addition compounds.  
Preferred compounds of formula (I) are those wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen such as, for example, 1-amino-3-ethyl-5,7-dimethyl adamantane, and compounds wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen such as, for example, 1-amino-3-cyclohexyl adamantane and 1-amino-3-ethyl adamantane.

Additional preferred compounds are those wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen such as, for example, 1-amino-3-methyl-5-propyl or 5-butyl adamantane, 1-amino-3-methyl-5-hexyl or cyclohexyl adamantane, or 1-amino-3-methyl-5-phenyl adamantane.

Especially preferred compounds are 1-amino-3,5-dimethyl adamantane, 1-amino-3,5-diethyl adamantane, i.e., compounds wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen, and compounds wherein R<sub>1</sub> and R<sub>5</sub> are hydrogen, R<sub>2</sub> is methyl or ethyl, and R<sub>3</sub> and R<sub>4</sub> are methyl such as, for example, 1-N-methylamino-3,5-dimethyl adamantane and 1-N-ethylamino-3,5-dimethyl adamantane.

The adamantane derivatives of formula (I) may be applied as such or in the form of their pharmaceutically-acceptable acid addition salts including, for example, the hydrochlorides, hydrobromides, sulfates, acetates, succinates or tartrates, or their acid addition salts with fumaric, maleic, citric, or phosphoric acids.

The compounds of formula (I) are administered in suitable form in doses ranging from about 0.01 to 100 mg/kg. Appropriate presentation forms are, for example, combinations of the active substance with common pharmaceutical carriers and adjuvants in the form of tablets, coated tablets, and sterile solutions or suspensions for injection. Pharmaceutically-acceptable carriers are, for example, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, gum arabic, corn starch, or cellulose, combined with diluents such as water, polyethylene glycol, etc. Solid presentation forms are prepared according to common methods and may contain up to 50 mg of the active ingredient per unit.

The efficacy of the compounds of formula (I) is described in the following pharmacological tests.

#### A. Displacement of TCP Binding

Phencyclidine (PCP), a known NMDA antagonist, binds to the NMDA receptor-associated ionic channel and blocks ionic transport (Garthwaite & Garthwaite, *Neurosci. Lett.* 83, 1987, 241-246). Additionally, PCP has been shown to prevent the destruction of brain cells after cerebral ischemia in rats (Sauer et al., *Neurosci. Lett.* 91, 1988, 327-332).

The interaction between compounds of formula (I) and the PCP bond is studied in the following. In this test 3H-TCP, a PCP analogue, is used.

A membrane preparation of rat cortex is incubated with 3H-TCP which is an analogue of phencyclidine (PCP) (Quinon & Pert 1982, *Eur. J. Pharmacol.* 83:155).

The interaction with the TCP binding is assessed for test compound no. 1 (1-amino-3,5-dimethyl adaman-tane) in a competitive experiment. This test shows that compound no. 1 is very effective in displacing TCP from the bond. The  $IC_{50}$  value is 89 nM. The conclusion can be drawn that compound no. 1 binds to NMDA receptor channels at the same site as the NMDA antagonist PCP.

#### B. Blocking of NMDA Receptor Channels

In the following test it is shown that the compounds of formula (I) according to the invention are as effective as PCP in blocking the NMDA receptor channel.

In the patch-clamp experiment, the current flowing through NMDA-activated membrane channels of cultured spinal marrow neurons (mouse) is measured (Hamill et al 1981, Philpotts Arch. 312: 85-100). After application of 20  $\mu$ M NMDA, the current signal of the cell is integrated for 20 sec. and recorded as a control answer ( $A_c$ ). During succeeding application of 20  $\mu$ M NMDA and 6  $\mu$ M of an adamantane derivative, the intensity of the substance effect can be determined as a relative change of the control answer ( $A/A_c - A =$  test answer).

The results are summarized in the following Table 1:

TABLE 1

Compound no.	1-Ac	n
1	0.66 $\pm$ 0.05	14
2	0.44 $\pm$ 0.08	7
3	0.58 $\pm$ 0.07	7
4	0.50 $\pm$ 0.11	5
5	0.56 $\pm$ 0.07	7
6	0.38 $\pm$ 0.05	7
7	0.25 $\pm$ 0.04	11
8	0.50 $\pm$ 0.03	6
PCP	0.50 $\pm$ 0.04	7
MK-801	0.60 $\pm$ 0.05	22

The values are given as means  $\pm$  SEM.

As can be seen from the results, the aminoadamantane derivatives of formula (I) are able to block the NMDA receptor channel as has been described for PCP (Ber-tolini et al, Neurosci. Lett. 84, 1988, 351-355) and for 5-methyl-10,11-dihydro-5H-dibenz[*a,d*]cycloheptene-5,10-imine (MK-801) (EP-A 0 264 183).

#### C. Anticonvulsive Effect

4, 12, 36, 108 and 324 mg/kg of the test substance is administered to mice by the intraperitoneal route (5 animals per dose). The supermaximum electroshock test is applied forty (40) minutes after application of the substance to investigate the anti-convulsive potential of the substance. The protected animals are added up over all dosages (score; maximum=25 animals).

The results are given in the following Table 2.

TABLE 2

Compound no.	Anticonvulsive action (score)	Mean (mg/kg)	ED <sub>50</sub> (mg/kg)
1	18		
	16		
	15	16.3	16
2	15		
	14		
	12	13.7	30
4	16		
	16		
	11	14.3	24
5	17		

TABLE 2-continued

Compound no.	Anticonvulsive action (score)	Mean (mg/kg)	ED <sub>50</sub> (mg/kg)
17	17	17.0	13
Standards:			
PCP	19	19.0	9
MK-801	25	25.0	<1

The ED<sub>50</sub> values were estimated according to Litchfield, J. T. and Wilcoxon, F., J. Pharmacol. Exp. Therap. 36, 99-113 (1949).

As can be seen from the above results, aminoadamantane derivatives of formula (I) exhibit a protective effect against electrically induced convulsions. They therefore have an anticonvulsive effect.

#### D. Correlation Between Channel-Blocking and Anticonvulsive Action

The correlation between the action of the tested adamantane derivatives 1-8 at the NMDA receptor channel (in vitro) and the anticonvulsive effect (in vivo) has been tested. For this purpose an xy diagram of both test parameters is plotted. It shows that there is a correlation between the blocking of the NMDA receptor channel and the anticonvulsive action of the adamantanes of formula (I).

#### E. Protection Against Cerebral Ischemia

Both carotid arteries are occluded in rats for 10 minutes. At the same time the blood pressure is reduced to 60-80 mm Hg by withdrawal of blood (Smith et al. 1984, Acta Neurol. Scand. 69: 385, 401). The ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood. After seven days the brains of the test animals are histologically examined for cellular changes in the CA1-CA4 region of the hippocampus, and the percentage of destroyed neurons is determined. The action of test compound No. 1 is determined after a single administration of 5 mg/kg and 20 mg/kg one (1) hour prior to the ischemia.

The results are summarized in the following Table 3:

TABLE 3

Area	Test compound no. 1		
	Control	5 mg/kg (n = 5)	20 mg/kg (n = 6)
CA1	80.2 $\pm$ 1.5	83.0 $\pm$ 2.2	53.1 $\pm$ 6.1**
CA3	3.6 $\pm$ 1.1	7.3 $\pm$ 1.8	2.7 $\pm$ 1.0
CA4	1.4 $\pm$ 0.4	3.7 $\pm$ 1.7	0.6 $\pm$ 0.3

The values are given in percent of damaged neurons  $\pm$  SEM.

Significance of the mean difference: \*\*p < 0.01 (U test)

The results show that the reduction of the post-ischemic neuronal brain damage in the CA1 region of the rat hippocampus is statistically significant after the pre-ischemic application of 20 mg/kg of test compound no. 1. Physiological parameters (e.g. blood pressure, body temperature) are not affected by the treatment. Moreover, the results show that the compounds according to formula (I) exhibit a neuroprotective action in cerebral ischemia.

Essentially the same result is attained by employing the compounds of the other Examples, especially those designated test compounds 2-8.

#### F. Protection Against NMDA-Induced Mortality

It is well known that, subsequent to cerebral ischemia, glutamate and aspartate levels increase massively in the brain. These excitatory aminoacids overstimulate

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the NMDA-subtype of the glutamate receptor thus leading to delayed neuronal death. A similar pathophysiological situation is obtained when mice are administered intraperitoneally with 200 mg/kg NMDA. This high dose will eventually cause 100% mortality in the animals (Leander et al. 1984, Brain Res. 448, 115-120). We have found that the adamantane derivatives of the present invention are protective against the NMDA-induced mortality.

Compound No.	Dose mg/kg	Protected Animals
1	50	8/8
	25	6/8
	10	3/8
3	50	6/8
	25	4/8
4	50	7/8
	25	5/8
5	25	5/8

In the control animals, to which no adamantane was administered, the mortality was eight (8) animals out of eight (8).

#### G. Displacement of [<sup>3</sup>H] MK-801 Binding in Human Brain Tissue

MK-801 binds to the ion channel associated with the NMDA receptor, as well as TCP does. This binding site is thought to mediate the neuroprotective effects of non-competitive NMDA-antagonists.

We have investigated whether the adamantane derivatives of the present invention are active at the MK-801 binding site. Tissue from frontal cortex was taken from patients at autopsy and homogenates were prepared. Inhibition of specific [<sup>3</sup>H] MK-801 binding (3 nM) by the test compounds was determined (see e.g. Kornhuber et al. 1989, Eur. J. Pharmacol. 166: 589-590).

The test compounds were highly potent in displacing MK-801 binding, thus indicating a specific interaction with the NMDA receptor channel and predicting neuroprotective properties.

Compound No.	K <sub>i</sub> nM
1	536
3	598
4	189
5	1607

wherein K<sub>i</sub> is the inhibition constant and nM is nanomoles per liter. Mean values from triplicate experiments are given  $\pm$  S.E.M.

The inhibition constant K<sub>i</sub> is approximately equal to the concentration of the adamantane in nM required to displace 50% of the MK-801 specifically bound to the receptor. In this regard, memantine (Compound No. 1) was found to be the most potent compound subjected to this test, when compared with thirteen (13) other clinically-used and centrally-acting drugs, as reported in the foregoing publication.

The invention is further described by the following illustrative examples, which are not to be construed as limiting:

#### EXAMPLE 1

##### Injectable Solution

For preparing a 0.5% solution, dissolve 0.5% active ingredient and 0.8% sodium chloride (DAB 9) in doubly distilled water. Filter the solution through an anti-

microbial filter, fill into 2-ml ampoules and sterilize for 20 minutes at 120° C. in an autoclave.

#### EXAMPLE 2

##### Solution

Dissolve 1% of active agent in demineralized water. Filter the solution before filling.

#### EXAMPLE 3

##### Tablets

1 tablet contains:	
Active ingredient	100 mg
Lactose	67.5 mg
Microcrystalline cellulose	18.0 mg
Talc	4.5 mg
	100.0 mg

The substances are mixed and the mixture compressed into 100-mg tablets in a direct tableting procedure without granulation.

#### EXAMPLE 4

##### Coated Tablets

Prepare 6-mm tablet cores of 100 mg as described under "Tablets". Coat the tablets in a sugar-coating process by coating the core with a sugar suspension first, followed by staining with a colored syrup and polishing.

The tablet coating consists of:

Sugar	65.0 mg
Talc	39.0 mg
Calcium carbonate	13.0 mg
Gum arabic	6.5 mg
Corn starch	3.7 mg
Shellac	1.1 mg
Polyethylene glycol 6000	0.2 mg
Magnesium stearate	1.3 mg
Dye	0.2 mg
	130.0 mg

Total tablet weight: 230 mg

#### EXAMPLE 5

For preparing a 0.01% infusion solution, dissolve 0.01% of active ingredient and 5% levulose in doubly-distilled water. Filter the solution through an antimicrobial filter, fill into 500-ml infusion bottles, and sterilize. The example provides 50 mg of active substance per single dose.

#### EXAMPLE 6

##### Synthesis of 1-Amino-3-isopropyl Adamantane Hydrochloride (Test Compound No. 3)

A. Preparation of Adamantane Methyl Carboxylate (1)  
 Stir 1.0 mol of adamantane carboxylic acid in 600 ml of methanol. Under ice cooling, drop 1.53 mol of acetyl chloride into the solution within 1 h. Remove the ice bath, and allow the reaction mixture to reach room temperature. Subsequently, heat for 3 hrs under reflux. Evaporate the reaction mixture to dryness under vacuum and distill. (Yield: 97%).

## B. Preparation of Isopropyl Adamantane (II)

Introduce 0.5 mol of magnesium chips into 50 ml of absolute ether, and drop 0.5 mol of methyl iodide into the solution under moisture-free conditions until the ether boils. Subsequently, heat in a water bath until the magnesium has completely dissolved. Into this solution at room temperature drop 0.2 mol of adamantane methyl carboxylate in absolute ether. Then heat to reflux for 3 hours. After cooling, hydrolyze with ice and mix with ammonium chloride solution until the precipitate has dissolved. Separate the ether phase, wash the aqueous phase with 2 portions of ether, and wash the combined organic phases with sodium bicarbonate solution. Then dry and evaporate to dryness under vacuum. (Yield: 93%).

## C. Preparation of Isopropene Adamantane (III)

Stir 0.25 mol of isopropyl adamantane (II) in 500 ml acetic anhydride for 12 hours at 160° C. Subsequently, pour the reaction mixture onto 1 liter of ice water and extract with ether. Dry the combined organic phases with magnesium sulfate, filter, and evaporate to dryness under vacuum. Distill the residue under vacuum. (Yield: 66%).

## D. Preparation of Isopropyl Adamantane (IV)

Dissolve 0.074 mol of adamantyl isopropene (III) in 100 ml of absolute ethanol. Add 4 g of palladium (5% on activated carbon) and hydrate under stirring for 24 hrs at room temperature. Subsequently, filter off the catalyst, and remove the solvent under vacuum. (Yield: 91%).

## E. Preparation of 1-Bromo-3-isopropyl Adamantane (V)

Mix 0.034 mol of isopropyl adamantane (IV) with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 h. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until the aqueous solution has discolored. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

## F. Preparation of 1-N-formyl-3-isopropyl Adamantane (VI)

Heat 0.028 mol of 1-bromo-3-isopropyl adamantane (V) with 40 ml of formamide to reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

## G. Preparation of 1-Amino-3-isopropyl Adamantane Hydrochloride

Mix 0.023 mol of 1-N-formyl-3-isopropyl adamantane (VI) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

## EXAMPLE 7

## Synthesis of 1-Amino-3-cyclohexyl Adamantane Hydrochloride (Test Compound No. 7)

## A. Preparation of 1-Phenyl Adamantane (I)

Heat 0.068 mol of iron(III) chloride to boiling in 20 ml of absolute benzene. Drop 0.0186 mol of 1-bromo-adamantane, dissolved in 30 ml of absolute benzene, to the solution. Then heat to boiling for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract the aqueous phase with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 80%).

## B. Preparation of 1-Hydroxy-3-phenyl Adamantane (II)

To a solution of 0.03 mol chrominitrioxide in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-phenyl adamantane at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture onto water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolyze the residue with 20 ml of 2N NaOH and 50 ml of methanol. Subsequently, remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).  
Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629-35.

## C. Preparation of 1-Bromo-3-phenyl Adamantane (III)

Stir 0.03 mol of 3-phenyl adamantanol (II) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and 30 min at room temperature. Subsequently, dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).  
Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

## D. Preparation of 1-N-formyl-3-phenyl Adamantane (IV)

Heat 0.03 mol of 1-bromo-3-phenyl adamantane (III) with 50 ml of formamide for 12 hrs to reflux. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 80%).

## E. Preparation of 1-Amino-3-phenyl Adamantane Hydrochloride (V)

Heat 0.02 mol of 1-N-formyl-3-phenyl adamantane (IV) with 100 ml of 15% hydrochloric acid at reflux for 24 hours. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

## F. Preparation of 1-Amino-3-cyclohexyl Adamantane (VI)

Dissolve 0.011 mol of 1-amino-3-phenyl adamantane (V) in 150 ml glacial acetic acid, mix with 0.3 g of platinum oxide (1% on activated carbon) and hydrate in a

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Pair apparatus at 35° C. at a hydrogen pressure of 3 bar. Subsequently, remove the catalyst by filtration and evaporate the filtrate to dryness. Take up the residue in methanol and precipitate the product with ether. Stick off and dry. (Yield: 70%).

#### EXAMPLE 8

##### Synthesis of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (Test Compound No. 8)

##### A. Preparation of 1-Bromo-3,5-dimethyl Adamantane (I)

Mix 0.5 mol of 1,3-dimethyl adamantane with a ten times excess of bromine (5 mol). Slowly heat and stir for 4 hrs under reflux. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

##### B. Preparation of 1-(2-Bromoethyl)-3,5-dimethyl Adamantane (II)

Mix 1.4 mol of 1-bromo-3,5-dimethyl adamantane (I) in hexane with 0.6 mol of aluminum bromide at -75° C. Subsequently, pass ethylene through the solution for 20-30 minutes, stir for 5 min, and pour the reaction mixture onto ice water. Extract with ether, dry the organic phase and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 48%).

##### C. Preparation of 1,3-Dimethyl-5-ethyl Adamantane (III)

Dissolve 0.5 mol of 1-(2-bromoethyl)-3,5-dimethyl adamantane (II) in toluene, mix with 0.55 mol of sodium-bis(2-methoxy-ethoxy)dihydro aluminate, and heat to boiling for 3 hrs. After hydrolysis, separate the organic phase, dry with magnesium sulfate, and evaporate to dryness under vacuum. Purify the residue by vacuum distillation. (Yield: 86%).

##### D. Preparation of 1-Bromo-3,5-dimethyl-7-ethyl Adamantane (IV)

Mix 0.4 mol of 1,3-dimethyl-5-ethyl adamantane (III) with a ten times excess of bromine (4 mol). Heat slowly and stir for 4 hrs under reflux. Subsequently allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 86%).

##### E. Preparation of 1-N-formyl-3,5-dimethyl-7-ethyl Adamantane (V)

Heat 0.2 mol of 1-bromo-3,5-dimethyl-7-ethyl adamantane (IV) with 150 ml of formamide at reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

##### F. Preparation of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (VI)

Mix 0.2 mol of 1-N-formyl-3,5-dimethyl-7-ethyl adamantane (V) with 100 ml of 15% hydrochloric acid and

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heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

#### EXAMPLE 9

##### Synthesis of 1-N-methylamino-3,5-dimethyl Adamantane (Test Compound No. 5)

Dissolve 0.1 mol of the appropriately substituted amino adamantane (1-amino-3,5-dimethyl adamantane) with 0.15 mol of chloromethyl formate and potassium carbonate in acetone and heat to reflux for 8 hrs. After cooling, filter the solution, remove the solvent and dry the residue. Mix the raw product (0.05 mol) with 0.1 mol of sodium-bis(2-methoxy-ethoxy)-dihydro aluminate in toluene and heat at reflux for 3 hrs. After cooling, hydrolyze with dilute HCl, dry the organic phase and evaporate to dryness. Purify the raw material by distillation.

#### EXAMPLE 10

##### Synthesis of 1-Amino-3-ethyl-5-phenyl Adamantane A. Preparation of 1-Bromo-3-ethyl Adamantane (I)

Mix 0.034 mol of ethyl adamantane with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 hrs. Then allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Subsequently extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

##### B. Preparation of 1-Ethyl-3-phenyl Adamantane (II)

Heat 0.068 mol of iron(II) chloride in 20 ml of absolute benzene to boiling. Drop 0.0186 mol of 1-bromo-3-ethyl adamantane (I), dissolved in 30 ml of absolute benzene, into the solution. Then heat at reflux for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 80%).

##### C. Preparation of 1-Ethyl-3-hydroxy-5-phenyl Adamantane (III)

To a solution of 0.03 mol of chromiuntrioxide, in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-ethyl-3-phenyl adamantane (II) at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture into water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolyze the residue with 20 ml of 2N NaOH and 50 ml of methanol. Remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629-35.

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D. Preparation of 1-Bromo-3-ethyl-5-phenyl  
Adamantane (IV)

Stir 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (III) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and for 30 min at room temperature. Subsequently dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

E. Preparation of 1-N-formyl-3-ethyl-5-phenyl  
Adamantane (V)

Heat 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (IV) with 50 ml of formamide for 12 hrs at reflux. After cooling, pour the reaction mixture into water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness. (Yield: 80%).

F. Preparation of 1-Amino-3-ethyl-5-phenyl  
Adamantane Hydrochloride (VI)

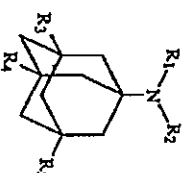
Heat 0.02 mol of 1-N-formyl-3-ethyl-5-phenyl adamantane (V) with 100 ml of 15% hydrochloric acid for 24 hrs at reflux. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

It is thus seen that certain adamantane derivatives, some of which are novel, have been provided for the prevention and treatment of cerebral ischemia, and that pharmaceutical compositions embodying such an adamantane derivative have been provided for use in the prevention and treatment of cerebral ischemia, the amount of the said adamantane derivative provided in either case being a cerebral ischemia-alleviating or preventive amount.

Various modifications and equivalents will be apparent to one skilled in the art and may be made in the compounds, compositions, methods, and procedures of the present invention without departing from the spirit or scope thereof, and it is therefore to be understood that the invention is to be limited only by the full scope which can be legally attributed to the appended claims.

We claim:

1. A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



(I)

wherein  
R<sub>1</sub> and R<sub>2</sub> are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein  
R<sub>3</sub> and R<sub>4</sub> are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein  
R<sub>5</sub> is hydrogen or a straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl group,

or a pharmaceutically-acceptable salt thereof.

2. A method according to claim 1, wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen.

3. A method according to claim 2, wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen, and R<sub>3</sub> and R<sub>4</sub> are methyl.

4. A method according to claim 2, wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen, and R<sub>3</sub> and R<sub>4</sub> are ethyl.

5. A method according to claim 1, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen, and R<sub>3</sub> is ethyl, isopropyl, or cyclohexyl.

6. A method according to claim 1, wherein R<sub>2</sub> and R<sub>5</sub> are hydrogen.

7. A method according to claim 6, wherein R<sub>3</sub> and R<sub>4</sub> are methyl, R<sub>2</sub> and R<sub>5</sub> are hydrogen and R<sub>1</sub> is methyl or ethyl.

8. A method according to claim 1, wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen.

9. A method according to claim 8, wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen, R<sub>3</sub> is ethyl, and R<sub>5</sub> and R<sub>4</sub> are methyl.

10. A method according to claim 1 for the treatment of Alzheimer's disease.

11. A method of claim 1, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventive amount.

12. A method of claim 11, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

13. A method of claim 11, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

\* \* \* \*

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UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION

PATENT NO. : 5,061,703 C1  
APPLICATION NO. : 90/007176  
DATED : November 7, 2006  
INVENTOR(S) : Joachim Bormann et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, line 56: delete "wherein" and substitute --*wherein*--.

Claim 1, line 57: delete "*R<sub>4</sub> and*" and substitute --*R<sub>4</sub> and*--.

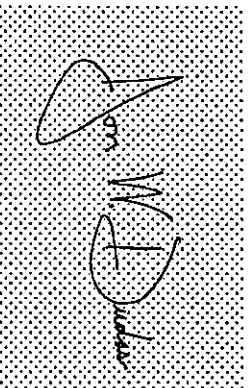
Claim 1, line 58: delete "*simultaneously*;" and substitute --*simultaneously*--.

Claim 10, line 62: delete "*disease wherein*" and substitute --*disease, wherein*--.

Claim 18, line 64: delete "*in*" and substitute --*is*--.

Signed and Sealed this

Fifth Day of June, 2007

A rectangular box containing a handwritten signature in black ink. The signature appears to be "Jon W. Dudas" written in a cursive, stylized script.

JON W. DUDAS  
*Director of the United States Patent and Trademark Office*

# EXHIBIT B



(12) **EX PARTE REEXAMINATION CERTIFICATE (5595th)**  
**United States Patent**  
Bormann et al.

(10) Number: **US 5,061,703 C1**  
(45) Certificate Issued: **Nov. 7, 2006**

(54) **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

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(73) Assignee: Merz Pharma GmbH & Co. KGaA,  
Frankfurt am Main (DE)

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(51) Int. Cl.  
*A61K 31/55* (2006.01)  
*A61K 31/445* (2006.01)  
*A61K 31/41* (2006.01)

(52) U.S. Cl. .... 514/212.01; 514/325; 514/359  
(58) Field of Classification Search ..... 514/212.01,  
514/325, 359

See application file for complete search history.

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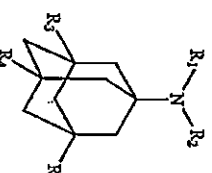
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(Continued)

Primary Examiner—Kevin E. Weddington

(57) ABSTRACT

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula



(I)

wherein

R<sub>1</sub> and R<sub>2</sub> are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R<sub>3</sub> and R<sub>4</sub> are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R<sub>5</sub> is hydrogen or a straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl group,  
or a pharmaceutically-acceptable salt thereof, is disclosed.

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# EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS  
INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in *italics* indicates additions made to the patent.

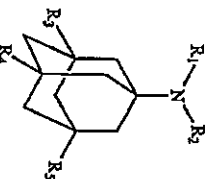
AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1 and 10 are determined to be patentable as amended.

Claims 2-9 and 11-13, dependent on an amended claim, are determined to be patentable.

New claims 14-19 are added and determined to be patentable.

1. A method for the prevention or treatment of cerebral ischemia comprising the step of orally administering, to a patient *diagnosed with Alzheimer's disease and in need thereof*, an effective amount of an adamantane derivative of the general formula



wherein

$R_1$  and  $R_2$  are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

$R_3$  and  $R_4$  are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

$R_5$  is hydrogen or a straight or branched  $C_1-C_6$  alkyl group; and

wherein

$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_5$  do not all represent hydrogen simultaneously;

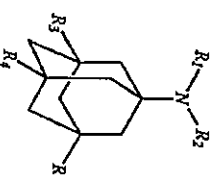
or a pharmaceutically-acceptable salt thereof.

10. A method according to claim 1 for the treatment of Alzheimer's disease wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.

14. A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an

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effective amount of an adamantane derivative of the general formula



wherein

$R_1$  and  $R_2$  are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

$R_3$  and  $R_4$  are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

$R_5$  is hydrogen or a straight or branched  $C_1-C_6$  alkyl group; and

wherein

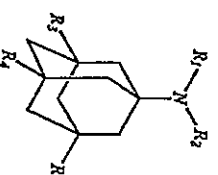
$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_5$  do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

15. The method of claim 14, wherein said adamantane derivative is memantine.

16. The method of claim 14, wherein said effective amount is from about 0.01 to 100 mg/kg.

17. A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

$R_1$  and  $R_2$  are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

$R_3$  and  $R_4$  are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

$R_5$  is hydrogen or a straight or branched  $C_1-C_6$  alkyl group; and

wherein

$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_5$  do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

18. The method of claim 17, wherein said adamantane derivative is memantine.

19. The method of claim 17, wherein said effective amount is from about 0.01 to 100 mg/kg.

\* \* \* \*

JS 44 (Rev. 11/04)

## CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

<b>I. (a) PLAINTIFFS</b> Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA and Merz Pharmaceuticals GmbH <b>(b) County of Residence of First Listed Plaintiff</b> (EXCEPT IN U.S. PLAINTIFF CASES)  <b>(c) Attorney's (Firm Name, Address, and Telephone Number)</b> Jack B. Blumenfeld, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, 1201 North Market Street, P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200	<b>DEFENDANTS</b> Apotex Inc. and Apotex Corp.  County of Residence of First Listed Defendant (IN U.S. PLAINTIFF CASES ONLY)  NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.  Attorneys (If Known)
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<b>II. BASIS OF JURISDICTION</b> (Place an "X" in One Box Only)  <input type="checkbox"/> 1 U.S. Government Plaintiff <input type="checkbox"/> 2 U.S. Government Defendant <input checked="" type="checkbox"/> 3 Federal Question (U.S. Government Not a Party) <input type="checkbox"/> 4 Diversity (Indicate Citizenship of Parties in Item III)	<b>III. CITIZENSHIP OF PRINCIPAL PARTIES</b> (Place an "X" in One Box for Plaintiff and One Box for Defendant) (For Diversity Cases Only)  <table style="width: 100%;"> <tr> <th></th> <th>PTF</th> <th>DEF</th> <th></th> <th>PTF</th> <th>DEF</th> </tr> <tr> <td>Citizen of This State</td> <td><input type="checkbox"/> 1</td> <td><input type="checkbox"/> 1</td> <td>Incorporated or Principal Place of Business In This State</td> <td><input type="checkbox"/> 4</td> <td><input type="checkbox"/> 4</td> </tr> <tr> <td>Citizen of Another State</td> <td><input type="checkbox"/> 2</td> <td><input type="checkbox"/> 2</td> <td>Incorporated and Principal Place of Business In Another State</td> <td><input type="checkbox"/> 5</td> <td><input type="checkbox"/> 5</td> </tr> <tr> <td>Citizen or Subject of a Foreign Country</td> <td><input type="checkbox"/> 3</td> <td><input type="checkbox"/> 3</td> <td>Foreign Nation</td> <td><input type="checkbox"/> 6</td> <td><input type="checkbox"/> 6</td> </tr> </table>		PTF	DEF		PTF	DEF	Citizen of This State	<input type="checkbox"/> 1	<input type="checkbox"/> 1	Incorporated or Principal Place of Business In This State	<input type="checkbox"/> 4	<input type="checkbox"/> 4	Citizen of Another State	<input type="checkbox"/> 2	<input type="checkbox"/> 2	Incorporated and Principal Place of Business In Another State	<input type="checkbox"/> 5	<input type="checkbox"/> 5	Citizen or Subject of a Foreign Country	<input type="checkbox"/> 3	<input type="checkbox"/> 3	Foreign Nation	<input type="checkbox"/> 6	<input type="checkbox"/> 6
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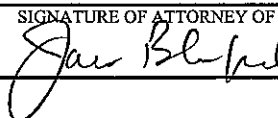
IV. NATURE OF SUIT (Place an "X" in One Box Only)				
<b>CONTRACT</b> <input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment <input type="checkbox"/> 151 Medicare Act <input type="checkbox"/> 152 Recovery of Defaulted Student Loans (Excl. Veterans) <input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits <input type="checkbox"/> 160 Stockholders' Suits <input type="checkbox"/> 190 Other Contract <input type="checkbox"/> 195 Contract Product Liability <input type="checkbox"/> 196 Franchise	<b>TORTS</b> <b>PERSONAL INJURY</b> <input type="checkbox"/> 310 Airplane <input type="checkbox"/> 315 Airplane Product Liability <input type="checkbox"/> 320 Assault, Libel & Slander <input type="checkbox"/> 330 Federal Employers' Liability <input type="checkbox"/> 340 Marine <input type="checkbox"/> 345 Marine Product Liability <input type="checkbox"/> 350 Motor Vehicle <input type="checkbox"/> 355 Motor Vehicle Product Liability <input type="checkbox"/> 360 Other Personal Injury  <b>PERSONAL INJURY</b> <input type="checkbox"/> 362 Personal Injury - Med. Malpractice <input type="checkbox"/> 365 Personal Injury - Product Liability <input type="checkbox"/> 368 Asbestos Personal Injury Product Liability  <b>PERSONAL PROPERTY</b> <input type="checkbox"/> 370 Other Fraud <input type="checkbox"/> 371 Truth in Lending <input type="checkbox"/> 380 Other Personal Property Damage <input type="checkbox"/> 385 Property Damage Product Liability	<b>FORFEITURE/PENALTY</b> <input type="checkbox"/> 610 Agriculture <input type="checkbox"/> 620 Other Food & Drug <input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881 <input type="checkbox"/> 630 Liquor Laws <input type="checkbox"/> 640 R.R. & Truck <input type="checkbox"/> 650 Airline Regs. <input type="checkbox"/> 660 Occupational Safety/Health <input type="checkbox"/> 690 Other  <b>LABOR</b> <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 730 Labor/Mgmt. Reporting & Disclosure Act <input type="checkbox"/> 740 Railway Labor Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl. Ret. Inc. Security Act	<b>BANKRUPTCY</b> <input type="checkbox"/> 422 Appeal 28 USC 158 <input type="checkbox"/> 423 Withdrawal 28 USC 157  <b>PROPERTY RIGHTS</b> <input type="checkbox"/> 820 Copyrights <input checked="" type="checkbox"/> 830 Patent <input type="checkbox"/> 840 Trademark  <b>SOCIAL SECURITY</b> <input type="checkbox"/> 861 HIA (1395ff) <input type="checkbox"/> 862 Black Lung (923) <input type="checkbox"/> 863 DIWC/DIWW (405(g)) <input type="checkbox"/> 864 SSID Title XVI <input type="checkbox"/> 865 RSI (405(g))  <b>FEDERAL TAX SUITS</b> <input type="checkbox"/> 870 Taxes (U.S. Plaintiff or Defendant) <input type="checkbox"/> 871 IRS—Third Party 26 USC 7609	<b>OTHER STATUTES</b> <input type="checkbox"/> 400 State Reapportionment <input type="checkbox"/> 410 Antitrust <input type="checkbox"/> 430 Banks and Banking <input type="checkbox"/> 450 Commerce <input type="checkbox"/> 460 Deportation <input type="checkbox"/> 470 Racketeer Influenced and Corrupt Organizations <input type="checkbox"/> 480 Consumer Credit <input type="checkbox"/> 490 Cable/Sat TV <input type="checkbox"/> 810 Selective Service <input type="checkbox"/> 850 Securities/Commodities/Exchange <input type="checkbox"/> 875 Customer Challenge 12 USC 3410 <input type="checkbox"/> 890 Other Statutory Actions <input type="checkbox"/> 891 Agricultural Acts <input type="checkbox"/> 892 Economic Stabilization Act <input type="checkbox"/> 893 Environmental Matters <input type="checkbox"/> 894 Energy Allocation Act <input type="checkbox"/> 895 Freedom of Information Act <input type="checkbox"/> 900 Appeal of Fee Determination Under Equal Access to Justice <input type="checkbox"/> 950 Constitutionality of State Statutes
<b>REAL PROPERTY</b> <input type="checkbox"/> 210 Land Condemnation <input type="checkbox"/> 220 Foreclosure <input type="checkbox"/> 230 Rent Lease & Ejectment <input type="checkbox"/> 240 Torts to Land <input type="checkbox"/> 245 Tort Product Liability <input type="checkbox"/> 290 All Other Real Property	<b>CIVIL RIGHTS</b> <input type="checkbox"/> 441 Voting <input type="checkbox"/> 442 Employment <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 444 Welfare <input type="checkbox"/> 445 Amer. w/Disabilities - Employment <input type="checkbox"/> 446 Amer. w/Disabilities - Other <input type="checkbox"/> 440 Other Civil Rights	<b>PRISONER PETITIONS</b> <input type="checkbox"/> 510 Motions to Vacate Sentence <b>Habeas Corpus:</b> <input type="checkbox"/> 530 General <input type="checkbox"/> 535 Death Penalty <input type="checkbox"/> 540 Mandamus & Other <input type="checkbox"/> 550 Civil Rights <input type="checkbox"/> 555 Prison Condition		

V. ORIGIN (Place an "X" in One Box Only)						
<input checked="" type="checkbox"/> 1 Original Proceeding	<input type="checkbox"/> 2 Removed from State Court	<input type="checkbox"/> 3 Remanded from Appellate Court	<input type="checkbox"/> 4 Reinstated or Reopened	<input type="checkbox"/> 5 Transferred from another district (specify)	<input type="checkbox"/> 6 Multidistrict Litigation	<input type="checkbox"/> 7 Appeal to District Judge from Magistrate Judgment

<b>VI. CAUSE OF ACTION</b>	Cite the U.S. Civil Statute under which you are filing (Do not cite jurisdictional statutes unless diversity): 35 U.S.C. § 271 Brief description of cause: patent infringement
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<b>VII. REQUESTED IN COMPLAINT:</b>	<input type="checkbox"/> CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23	DEMAND \$	CHECK YES only if demanded in complaint: JURY DEMAND: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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<b>VIII. RELATED CASE(S) IF ANY</b>	(See instructions): JUDGE <u>Sleet</u>	DOCKET NUMBER <u>08-21</u> <u>08-52</u>	<u>08-22</u> <u>08-291</u>
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DATE <u>June 5, 2008</u>	SIGNATURE OF ATTORNEY OF RECORD 			
FOR OFFICE USE ONLY				
RECEIPT #	AMOUNT	APPLYING IFP	JUDGE	MAG. JUDGE

## INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

## Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

**I. (a) Plaintiff's-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

**II. Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here. United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

**III. Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

**IV. Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

**V. Origin.** Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

**VI. Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. Do not cite jurisdictional statutes unless diversity. Example: U.S. Civil Statute: 47 USC 553

Brief Description: Unauthorized reception of cable service

**VII. Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction. Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

**VIII. Related Cases.** This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.